Summary of Research Activities by Disease Category

Cancer

Cancer research continues to move toward a new era of personalized medicine. Cancer is not a single disease, but a complex of diseases in which genetic changes disrupt molecular pathways. Patients with identical diagnoses may experience different symptoms, different responses to the same treatment, and ultimately different outcomes. A better understanding of the genetic glitches that cause the various diseases we call cancer can open the door for targeted treatment for each individual and enable more predictive and individualized approach to care. The recent identification of genetic mutations linked to breast, colorectal, and many other cancers has demonstrated the value and feasibility of pursuing more comprehensive knowledge of the molecular origins of cancer. In 2006, NIH initiated a pilot project designed to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies. Three years later, The Cancer Genome Atlas (TCGA) has identified many of the major genomic changes in hundreds of brain and ovarian tumors. Specifically, TCGA first characterized glioblastoma—an extremely deadly form of cancer—and revealed at least three genes involved in these tumors and four distinct subtypes. Importantly, the data generated are a community resource and thus made available in the public domain days after being produced by the research network. With that foundation of success, TCGA now is expanding to identify all of the relevant genomic alterations in 20 major tumor types in hopes of continuing this model of enabling the next generation of discovery that promises to improve cancer diagnosis, prevention, and care.

Introduction

Cancer—a leading cause of death among Americans, accounting for more than 560,000 deaths in 2007—is not a single disease. More than 100 types of cancer have been identified based on their association with different organs and cell types. However, within each type of cancer an individual's tumor can differ greatly due to complex biological factors. Cancer arises from alterations in the interactions among layered biological systems. The many different forms of cancer can be understood only by characterizing these systems and how they interact. NIH cancer research programs aim to improve our understanding of cancer as a multiscale, multidimensional disease system. This approach provides a context for research on: preventing cancer through risk assessment based on genetic susceptibilities and environmental exposures; detecting and diagnosing cancer based on knowledge of cancer signaling pathways and biomarkers; predicting cancer progression and outcomes based on examination of the tumor microenvironment and interactions between tumor cells and surrounding, noncancerous cells; developing personalized interventions for individual cancer patients based on predictions of their response to treatment; and addressing the unique needs of the growing number of cancer survivors.

To take full advantage of the scientific opportunities in cancer research, including the opportunities generated by the convergence of emerging technologies with advances in molecular sciences, an action plan has been created to ensure that the use of these new funds is optimally leveraged to understand and control cancer. *The NIH Strategic Plan to Double the NIH Cancer Research Budget* focuses on understanding the causes and mechanisms of cancer; accelerating progress in cancer prevention; improving early detection and diagnosis; developing effective and efficient treatments; understanding factors that influence cancer outcomes; improving the quality of cancer care; improving the quality of life for cancer patients, survivors, and their families; and overcoming cancer health disparities. Using cancer as a model that could inform basic biology and physiology of all diseases, NIH has developed a blueprint for 21st-century personalized medicine. This new investment plan extends the scope of cancer research to embrace scientists and clinicians working on other diseases who heretofore may not have been members of the oncology research community.

NIH has identified seven objectives related to cancer research to be supported with ARRA funds: (1) accelerating and expanding cancer research; (2) advancing personalized cancer treatment and prevention; (3) redesigning the cancer research bioinformatics infrastructure; (4) revamping the cancer clinical trials system; (5) fostering collaboration to increase the impact of cancer research; (6) strengthening the research workforce; and (7) improving care and quality of life for all cancer patients. NIH will use ARRA funds to support three signature cancer-related initiatives to accelerate cancer research and advance personalized medicine: the Cancer Genome Atlas (to support development of targeted prevention, detection, and treatment methods), the Physical Sciences-Oncology Centers Program (to improve understanding of cancer's causal pathways), and the Personalized Cancer Care/Drug Development Platform (to support development of individually tailored interventions).

As the NIH vision of personalized medicine evolves, doctors will be able to use detailed information about an individual's cancer and employ molecular and clinical data to guide the selection of therapies or preventive measures that are most likely to be safe and effective for that person. Personalized medicine promises to improve quality of life for cancer survivors, minimize adverse side effects of therapy, and reduce disparities among populations currently experiencing an excess burden of cancer.

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Cancer research is conducted by a number of ICs; however, most of the research investment is committed to NCI programs. Five NCI extramural divisions support research carried out at nearly 650 universities, hospitals, cancer centers, specialized networks and research consortia, and other sites throughout the United States and in more than 20 other countries. In addition, NCI provides infrastructure to help the greater cancer research community take advantage of the potential benefits of emerging technologies (e.g., genomics, proteomics, bioinformatics, and molecular imaging). NCI's two intramural divisions conduct basic, translational, clinical, and population research, making fundamental discoveries related to cancer causes and mechanisms, genetics, and host immunological and other responses to cancer and aim to rapidly translate those findings into novel preventive and detection methods and therapies.

Cancer research conducted or supported by other NIH ICs is wide-ranging and often coordinated with NCI programs and grantees—for example, the Surveillance, Epidemiology, and End Results (SEER) program (a source of information on cancer incidence and survival in the United States) and the nationwide network of Comprehensive Cancer Centers. Examples of cancer research within other ICs include:

- Fogarty International Center for Advanced Study in the Health Sciences (FIC): international studies and collaborations on cancer research
- National Eye Institute (NEI): research on cancers of the eye
- National Heart, Lung, and Blood Institute (NHLBI): research on blood-related cancers and support for breast, colorectal, and reproductive cancer as the administrative coordinator of the NIH Women's Health Initiative
- National Center for Complementary and Alternative Medicine (NCCAM): research on nontraditional approaches to cancer therapies across the cancer continuum
- National Human Genome Research Institute (NHGRI): epidemiological and genomic research on cancers
- National Center on Minority Health and Health Disparities (NCMHD): research on cancer in diverse populations
- National Institute on Aging (NIA): research on prostate and skin cancers and the biology of aging as it relates to cancer

- National Institute on Alcohol Abuse and Alcoholism (NIAAA): research on the role of alcohol in colorectal, breast, liver, and pancreatic cancers
- National Institute of Allergy and Infectious Diseases (NIAID): technology development in support of cancer research, diagnosis, and therapy and studies of the role of viruses in cancer
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS): research on skin and bone cancers
- National Institute of Biomedical Imaging and Bioengineering (NIBIB): imaging and bioinformatics technology development in areas that are vital to cancer research
- National Institute of Child Health and Human Development (NICHD): research on breast and reproductive cancers
- National Institute on Drug Abuse (NIDA): research on treatments for tobacco addiction serving as cancer prevention
- National Institute on Deafness and Other Communication Disorders (NIDCD): research on deafness and communication disorders in relation to head and neck cancers
- National Institute of Dental and Craniofacial Research (NIDCR): research on head and neck cancers
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): research on liver, prostate, kidney, colorectal, and bladder diseases and conditions that may lead to cancer
- National Institute of Environmental Health Sciences (NIEHS): research on the effects of biological, chemical, or physical agents on human health
- National Institute of General Medical Sciences (NIGMS): cancer-related basic biomedical research
- National Institute of Mental Health (NIMH): research on mood disorders in relation to cancer and cancer treatment
- National Institute of Neurological Disorders and Stroke (NINDS): research on brain, spinal cord, and pituitary cancers
- National Institute of Nursing Research (NINR): research across the cancer continuum

Burden of Illness and Related Health Statistics

Although significant progress has been made toward reducing the burden of cancer in America, cancer remains a leading cause of death, second only to heart disease—one of every four deaths is due to cancer.[1, 2] The economic cost of cancer in 2005 was estimated at more than $200 billion, including $74 billion in direct health care costs and more than $135 billion in indirect costs associated with lost productivity due to illness and premature death. The American Cancer Society estimated that, in 2009, there were about 1,479,350 new diagnoses of invasive cancer and 562,340 Americans died of cancer.[3] Moreover, the World Cancer Report indicates that cancer rates are set to increase at an alarming rate globally—specifically, they could further increase by 50 percent to 15 million new cases in the year 2020. Thus, cancer research is a major priority for NIH.[4]

There are signs of progress. U.S. death rates for the most common cancers and for all cancers combined have decreased significantly since 1995.[5] However, the annual number of cancer diagnoses is expected to almost double over the next 50 years, from 1.4 million to 2.6 million because of the growth and aging of the population. Increasing numbers of Americans are surviving cancer. NIH estimated that on January 1, 2005, 11.1 million living Americans had a history of invasive cancer.[6] Like cancer incidence, these numbers are likely to increase because of the anticipated growth and aging of the U.S. population.[7]

The most common cause of cancer-related death in the United States is lung cancer. The three most common cancers among men are prostate cancer, lung cancer, and colon cancer. For women, the three most frequently occurring cancers are breast, lung, and colon.[8]

Significant disparities in the U.S. burden of cancer have been documented through literature reviews,

program reviews, and ongoing research. These disparities are discussed in *Minority Health and Health Disparities* later in this chapter.

[1] For more information, see www.cancer.org.
[2] For more information, see www.cdc.gov/nccdphp/burdenbook2004/index.htm.
[3] American Cancer Society; 2009.
[4] National Cancer Institute. 2006 Fact Book. Bethesda, Md.: U.S. Department of Health and Human Services, 2007. For more information, see http://obf.cancer.gov/financial/attachments/06Factbk.pdf
[5] NCI; 2006.
[6] American Cancer Society. Facts and Figures 2009.
[7] Edwards BK, et al. *Cancer* 2002;94:2766-92. PMID: 12173348.
[8] NCI; 2006.

NIH Funding for Cancer Research

Actual NIH funding support levels for cancer research were $5,570 million in FY 2008, and $5,629 million and $1,120 million in FY 2009, respectively, for non-ARRA (regular appropriations) and ARRA (Recovery Act appropriations). Click on the funding levels, which are live links, to produce detailed project listings. These lists are derived from the NIH Research, Condition, and Disease Categorization (RCDC) system. In addition, the table at the end of this chapter indicates some of the research areas involved in this investment (see *Estimates of Funding for Various Research, Condition, and Disease Categories*).

Summary of NIH Activities

Across NIH, cancer and cancer-related research activities are focused on two overarching goals: preempting cancer at every opportunity and ensuring the best outcomes for all. Specific objectives related to these goals include:

Preempting cancer at every opportunity:

- Understanding the causes and mechanisms of cancer
- Accelerating progress in cancer prevention
- Improving early detection and diagnosis
- Developing effective and efficient treatments

Ensuring the best outcomes for all:

- Understanding the factors that influence cancer outcomes
- Improving the quality of cancer care
- Improving quality of life for cancer patients, survivors, and their families
- Overcoming disparities in cancer prevention, diagnosis, treatment, and outcomes

NIH also is exploiting the potential of emerging technologies (e.g., molecular imaging, nanotechnology, and bioinformatics) in cancer research and care and is building the research infrastructure needed to expand knowledge and put new insights into practice.

Preempting Cancer at Every Opportunity

Understanding the Causes and Mechanisms of Cancer

Research that improves our understanding of the causes and mechanisms of cancer—from identifying novel risk factors to elucidating the processes of metastasis (the spread of cancer from the primary tumor site)—is essential for the development and application of interventions to preempt cancer's initiation and progression. NIH's plan for deciphering the causes and mechanisms of cancer includes fundamental research into cell signaling that can provide important insights into the molecular regulators of cell growth and differentiation in a range of tissues. In addition, NIH supports studies in molecular epidemiology to define complex risk factors, research on the tumor macroenvironment and microenvironment, understanding the role of altered gene expression in cancer progression, and exploring the roles of susceptibility genes in cancer risk and initiation.

A primary challenge for NIH is dissecting the molecular basis of cancer. The Cancer Genome Atlas (TCGA) is developing a comprehensive catalogue of the genetic changes that occur in cancers. The genomic information generated by TCGA could fuel rapid advances in cancer research and suggest new therapeutic targets. It also could suggest new ways to categorize tumors, which might allow clinical trials to focus on those patients who are most likely to respond to specific treatments. The TCGA network has selected more than 6,000 gene and microRNA (miRNA) targets for sequencing that represent both protein-coding genes and miRNAs.

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The Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative identifies and validates therapeutic targets for childhood cancers beginning with acute lymphoblastic leukemia and neuroblastoma. Scientists involved in this initiative recently identified mutations in a class of protein kinase genes called the janus kinases that predict relapse in high-risk children with acute lymphoblastic leukemia.[9]

Genetic susceptibility to cancer and cancer risk associated with environmental exposures also are important research topics. Using powerful new technologies to scan the entire human genome, NIH is conducting genome-wide association studies (GWAS) to identify unsuspected genetic variants associated with cancer risk (also see the section on *Genomics* in Chapter 3 for more information about GWAS). The Cancer Genetic Markers of Susceptibility (CGEMS) project, for example, is designed to identify genes that increase the risk of breast and prostate cancers. Similar efforts are directed at cancers of the pancreas, bladder, lung, and other organs. The results of these GWAS promise to provide novel strategies for cancer detection, prevention, and treatment.

Another major NIH initiative is the Sister Study, which is investigating environmental and genetic risk factors for breast cancer. This study involves a cohort of 50,000 sisters of women who have had breast cancer. These unaffected sisters are being followed over time, with periodic health updates. The women who develop breast cancer during the follow-up period will be compared with those who remained healthy to identify factors associated with increased cancer risk.

NIH also is supporting a network of Breast Cancer and the Environment Research Centers (BCERCs) to study the impact of prenatal to adult environmental exposures that may predispose a woman to breast cancer. One of the goals of the BCERCs is to develop public health messages to educate young girls and women who are at high risk of breast cancer about the role of specific environmental stressors in breast cancer and how to reduce exposures to those stressors. NIEHS is an NIH partner in support of this initiative as part of its Partnerships for Environmental Public Health initiative.

Other research into the causes and mechanisms of cancer has revealed that tumors function like

organs, comprising many interdependent cell types that contribute to tumor development and progression. The relationship between tumors and their surrounding cellular environment evolves over time, strongly influencing tumor progression, metastatic potential, and responsiveness to treatment. The Tumor Microenvironment Network is a new NIH program focused on expanding our understanding of the role of the microenvironment in which a tumor originates and the critical role it plays during tumor development, progression, and metastasis.

Furthermore, interest is growing in the scientific community about the relationship between inflammation and cancer. Inflammation is a response to acute tissue damage, whether resulting from physical injury, infection, exposure to toxins, or other types of trauma. NIH actively is pursuing research on the linkages between carcinogenesis and alterations in the microenvironment induced by inflammation. Current research on inflammation suggests that pro-inflammatory conditions contribute to the development of several types of cancer, including lung, stomach, and liver cancers, and may lead to new treatment approaches (for example, research efforts focused on inflammatory and fibrotic diseases of the esophagus, stomach, colon, pancreas, and liver—all of which are risk factors for the development of cancer in these organs). The Cancer and Inflammation Program (CIP) constitutes a major component of NIH's inflammation and cancer initiative, which partners expertise in inflammation and immunology with cutting-edge cancer etiology and carcinogenesis research.

Systems biology and systems genetics also are promising new fields of study that will increase our understanding of the causes and mechanisms of cancer. These disciplines focus on biological and genetic networks that can be measured, modeled, and manipulated rather than focusing on the individual components. Because this research requires multidisciplinary teams of experts in biology, medicine, engineering, mathematics, and computer science, NIH launched the Integrative Cancer Biology Program (ICBP) to develop a framework for these activities. The ICBP has funded nine integrative biology centers around the United States to provide the nucleus for the design and validation of computational and mathematical models of cancer. Networks of genes can be found and their associations with cancer tested and quantified, and parallel association studies can be conducted in relevant human populations.

NIH is expanding its research portfolio related to the basic biology of tumor stem cells (also referred to as tumor-initiating cells). Tumor stem cells may be responsible for the recurrence of malignancy in some cancers. These cells often are resistant to standard chemotherapeutic agents but may contain unique target molecules that may allow their eradication with novel molecular therapeutics. Progress has been made in identifying tumor stem cells in multiple myeloma, acute myelogenous leukemia, and breast cancer.

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[9] Mullighan CG, et al. Proc *Natl Acad Sci U S A* 2009;106:9414-8. PMID: 19470474. PMCID: PMC2695045.

Accelerating Progress in Cancer Prevention

Current research efforts into preventing cancer focus on modifying behaviors that increase risk, mitigating the influence of genetic and environmental risk factors, and interrupting the cancer process through early medical intervention. Dramatic developments in technology and a more complete understanding of the causes and mechanisms of cancer will enable us to provide more effective ways to prevent the disease. Identifying critical molecular pathways in precancerous lesions will provide new drug targets for preempting cancer. Transdisciplinary research will provide a more complete

understanding of the interplay of molecular, behavioral, genetic, and other factors that contribute to cancer susceptibility. One example is the Partnerships for Environmental Public Health initiative, which is studying the health burden associated with risks in populations with inequities in environmental exposure and disease (including cancer); quantifying exposures to the many chemical, biological, and social stressors people experience over their lifetime at home, work, and play; and addressing health impacts of emerging environmental threats.

A major step forward in our efforts to prevent cancer has been the development of vaccines that target human papillomavirus (HPV). Persistent infection with HPV is recognized as the major cause of cervical cancer. Gardasil®, a U.S. Food and Drug Administration (FDA)-approved vaccine against HPV types 6, 11, 16, and 18—the viral types that cause approximately 70 percent of cervical cancers and 90 percent of genital warts—now is available. Other similar vaccines against HPV types 16 and 18 and/or additional subtypes are in development. These vaccines have the potential to save thousands of women's lives annually in the United States and several hundred thousand more each year worldwide. All of these vaccines resulted directly from epidemiological, basic, and preclinical research discoveries, as well as the development of a prototype HPV vaccine, by NIH scientists.

In an effort to reduce the cancer incidence, morbidity, and mortality associated with obesity, low physical activity, and poor diet, NIH has funded the Transdisciplinary Research on Energetics and Cancer (TREC) research centers, which foster collaboration among transdisciplinary teams of scientists. TREC centers are studying factors that lead to obesity and the mechanisms by which obesity increases the risk of cancer. The TREC initiative is connecting with a number of established initiatives in the areas of diet, physical activity, and weight and is integrated with the NIH Obesity Research Task Force Strategic Plan.

In an effort to reduce the cancer incidence, morbidity, and mortality associated with obesity, low physical activity, and poor diet, NIH has funded the Transdisciplinary Research on Energetics and Cancer (TREC) research centers, which foster collaboration among transdisciplinary teams of scientists.

Because most cases of lung cancer are caused by tobacco use and are, therefore, preventable, multiple NIH Institutes have co-funded seven Transdisciplinary Tobacco Use Research Centers (TTURCs), which seek to identify familial, early childhood, and lifetime psychosocial pathways associated with smoking initiation, use, cessation, and patterns of dependence. Research on the genetics of addiction, physiological biomarkers, and advanced imaging techniques should allow the development of individualized and community approaches to the prevention and treatment of tobacco-related diseases. The TTURC model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships.

We now know that the environment and behavioral lifestyles can play a critical role in the development of cancer. In fact, it was this discovery that led to a public health success story in the 20th century—the reduction in tobacco use and related diseases. By the mid-1950s, the mysterious and alarming epidemic in lung cancer, a disease that was almost nonexistent in 1900, was linked to smoking behavior. In the last decade, overall cancer death rates have dropped for the first time in a century, driven largely by the dramatic reduction in male smoking from 47 percent in the 1960s to less than 23 percent today. About 40 percent of this drop in overall cancer rates has been credited to the dramatic reduction in male smoking and male lung cancer deaths since 1991 (more than 146,000 fewer deaths during 1991 to 2003 alone). This success has been due to public-private partnerships and also is a trans-HHS victory, as significant research investments have been made over the last 50 years by NCI, NHLBI, NIDA, NIAAA, FIC, the Centers for Disease Control and Prevention (CDC), and the Agency for Healthcare Research and Quality (AHRQ). Without these investments, 40 million Americans might still be smoking today, hundreds of thousands of them would have died prematurely of a tobacco-related disease, and billions of dollars would have been spent on their treatment.[10]

The NIH-supported Community Clinical Oncology Program (CCOP) provides a network for greater participation in clinical trials on cancer prevention and treatment. There are 50 CCOPs and 13 Minority Based-CCOPs (CCOPs with 40 percent of their new patients from minority populations) currently funded in 35 states, the District of Columbia, and Puerto Rico. The program involves 3,645 physicians participating in 415 hospitals, working on more than 70 active prevention and control trials. The groups responsible for developing and implementing cancer prevention and control clinical trials are known as Research Bases; 14 Cooperative Groups and Cancer Centers have grants to serve as CCOP Research Bases.

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[10] Thun MJ, Jemal A. *Tob Control* 2006;15:345-7. PMID: 16998161.

Improving Early Detection and Diagnosis

Detecting and diagnosing tumors early in the disease process, before the tumor becomes invasive and metastatic, can dramatically improve a patient's odds for successful treatment and survival, and prevent a large proportion of cancer deaths. Therefore, NIH seeks to accelerate the translation of basic research findings into sophisticated, minimally invasive procedures that harness imaging, genomic, proteomic, nanotechnology, and other advanced early-detection and diagnostic techniques.

Molecular profiling is an ongoing effort at NIH, from work at the bench to larger initiatives. In the area of molecular diagnostics, NIH has formed the Early Detection Research Network (EDRN) to bring a collaborative approach to the discovery, development, and validation of early-detection biomarkers for clinical application. Another NIH program, Strategic Partnering to Evaluate Cancer Signatures (SPECS), focuses on confirming, evaluating, and refining "signatures" derived from the molecular analysis of tumors (i.e., biomarkers detection) to improve patient management and outcomes. In addition, the Cancer Genome Anatomy Project (CGAP) focuses on determining the gene expression profiles of normal, precancerous, and cancerous cells to improve detection, diagnosis, and treatment. The CGAP website makes tools for genomic analysis available to researchers worldwide.

Yet another area of research that holds promise for advancing molecular diagnostics is proteomics—the study of complex arrays of proteins produced by cells and tissues. The completion of the Human Genome Project in 2003 has been a major catalyst for proteomics research, and NIH has taken a leading role in facilitating the translation of proteomics from laboratory research to clinical application through the Clinical Proteomic Technologies for Cancer (CPTC) initiative. The overall objective of this initiative is to build the foundation of technologies (assessment, optimization, and development), data, reagents and reference materials, computational analysis tools, and infrastructure needed to systematically advance our understanding of protein biology in cancer and accelerate basic science research and the development of clinical applications. CPTC comprises three integrated programs: the Clinical Proteomic Technology Assessment for Cancer (CPTAC) network, the Advanced Platforms and Computational Sciences program, and the Proteomic Reagents and Resources Core.

Developing Effective and Efficient Treatments

Developing more effective, more efficient, and less toxic cancer treatments is at the heart of the NIH

cancer research agenda. A strong understanding of the fundamental mechanisms leading to cancer development, progression, and metastasis will dramatically improve the identification of key biochemical pathways in the disease process as targets for treatment. Acceleration of target validation and the development of new treatment modalities will be possible through recent advances in biomedical science and technology. Rapid translation from development to delivery will ensure that promising treatments move safely and efficiently from preclinical investigation through late-stage clinical trials and into clinical practice. NIH is taking a multipronged approach to developing new therapies for cancer.

One innovative initiative, the NCI Experimental Therapeutics Program (NExT), combines the extensive expertise of cancer treatment and diagnosis in anticancer drug development with the dynamic NIH intramural research resources. This collaboration will rely on recent guidance from FDA concerning exploratory studies of investigational new drugs. Through NExT, extramural and intramural teams have prioritized a pipeline of targeted therapeutics for development. NExT promises to shorten the timeline for moving anticancer drugs from the laboratory to the clinic.

Another program, the Cancer Imaging Program (CIP), supports cancer-related basic, translational, and clinical research in imaging sciences. CIP initiatives include the development and delivery of image-dependent interventions for malignant and premalignant conditions; standardized models for the design of clinical trials that use imaging technologies; development of emerging imaging technologies, including nanotechnology, proteomics, and high-throughput screening; and development of imaging methods for cancer detection and treatment and for monitoring responses to therapy.

NIH launched the Comparative Oncology Program (COP) in an effort to improve the translational research process. Its mission was to provide an integrated mechanism by which naturally occurring cancers in pet dogs could be used to generate new information about cancer, translate biological concepts toward clinical application, and bring novel therapeutic options to the management of human cancers. As part of this effort, COP has established a multicenter collaborative network of extramural comparative oncology programs to design and implement preclinical trials involving pet animals to evaluate novel therapeutic strategies for cancer.

Ensuring the Best Outcomes for All

Research on the quality of cancer care is essential to ensuring the best outcomes for all who may be affected by cancer. Research in this area can include surveillance as well as epidemiological and cost-effectiveness studies. In addition, quality-of-life research increases our understanding of the impact of cancer on patients, survivors, and their family members—many of whom are themselves at increased risk for cancer due to shared cancer-causing genes, lifestyles, or environmental exposures. Dissemination research helps ensure that the knowledge gained through NIH-supported research is appropriately and effectively communicated to health care providers, policymakers, and the public. An additional goal related to overcoming health disparities in cancer incidence and outcomes is described in a later section of this chapter (also see the section on *Minority Health and Health Disparities* in Chapter 2).

NIH currently is engaged in making cancer a working model for quality-of-care research and the translation of research findings into practice. To this end, several collaborative projects have been initiated: (1) an interagency working committee, the Quality of Cancer Care Committee, which has fostered collaborative projects directly involving the Health Resources and Services Administration, AHRQ, Centers for Medicare and Medicaid Services, Department of Veterans Affairs, Indian Health Service, CDC, and other Federal health care research and delivery agencies; (2) the National Quality Forum, a major public-private partnership, to identify core measures of cancer care quality; (3) research on outcomes measurement by the Cancer Outcomes Measurement Working Group and the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS); (4) studies on improving the

quality of cancer communications; and (5) research to monitor patterns of treatment dissemination and quality of care through Patterns of Care/Quality of Care Studies. In addition, the NCI Community Cancer Centers Program (NCCCP) is researching how best to bring effective cancer treatments to patients in the communities where they live.

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The population of cancer patients surviving more than 5 years continues to grow. NIH continues to support research and education aimed at professionals who deal with cancer patients and survivors. The Office of Cancer Survivorship addresses the physical, psychosocial, and economic impacts of cancer diagnosis and its treatment and the need for interventions to promote positive outcomes in survivors and their families. Important early findings suggest long latencies for treatment-related effects, highlighting the need for extended follow up, early identification, and intervention before complications become more serious.

To improve the outcomes of cancer patients, advances in knowledge must be effectively disseminated to the public and health care providers. The Cancer Control P.L.A.N.E.T. portal is a collaborative effort aimed at providing access to data and resources that can help cancer control planners, health educators, program staff, and researchers to design, implement, and evaluate evidence-based cancer control programs. P.L.A.N.E.T. assists local programs with resources that help them determine cancer risk and burden within their State and helps States identify potential partners. P.L.A.N.E.T. also provides online resources for interpreting research findings and recommendations and accessing products and guidelines for planning and evaluation.

Infrastructure for Research

NIH places a high priority on technology development (also see the section on *Technology Development* in Chapter 3) to support both research and the application of research findings to improve health care delivery, emphasizing the areas of bioinformatics, cancer imaging, proteomics, and nanotechnology. As NIH-supported scientists begin to apply new discoveries to cancer prevention, early detection, and treatment, it increasingly will be important to integrate the tools and insights of research, science, and technology as effectively as possible.

The Cancer Biomedical Informatics Grid® (caBIG®) is an important initiative designed to accelerate research discoveries and improve patient outcomes by supporting the sharing of data and tools among researchers, physicians, and patients throughout the cancer community. caBIG® has developed and freely distributed more than 40 software tools with applications in basic and clinical research on cancer and other diseases. NIH is committed to extending caBIG® across the broader cancer research and care community. More than 1,500 individuals, representing more than 450 organizations in 13 countries, have so far participated in caBIG® projects. caBIG® technologies have been used to link the 65 Cancer Centers, the Community Cancer Centers Program, The Cancer Genome Atlas, other NIH Institutes, FDA, and international partners.

The Cancer Biomedical Informatics Grid® (caBIG®) is an important initiative designed to accelerate research discoveries and improve patient outcomes by supporting the sharing of data and tools among researchers, physicians, and patients throughout the cancer community.

The proposed Cancer Human Biobank (caHUB) is envisioned as a unique, centralized, non-profit public resource to ensure an adequate supply of high-quality biospecimens and associated data acquired within an ethical framework. caHUB will promote standardization of biospecimen collection, distribution, data vocabulary, and informed consent, and will provide an integrated information technology system to support all functions related to biospecimens. The Cancer Genome Atlas will serve as a pilot project for caHUB specimen collection and processing.

The new BIG Health Consortium™ will be a public-private partnership among key stakeholders in health care: patient advocates, health care providers, payers, product innovators, investors, and information technologists. Its mission is to show how and why personalized medicine works. Through a series of demonstration projects, BIG Health™ will model a new approach in which clinical care, clinical research, and scientific discovery are linked. The key enabler for this linkage is the informatics infrastructure that NIH has already developed—caBIG®.

The Alliance for Nanotechnology in Cancer, a comprehensive endeavor involving both public and private sectors, is designed to accelerate the application of the best capabilities of nanotechnology to cancer research. This initiative supports research on novel nanodevices to detect and pinpoint the location of cancer at its earliest stages, deliver anticancer drugs specifically to malignant cells, and determine in real time whether these drugs are effective in killing those cells. Programs of the Alliance include the Nanotechnology Characterization Laboratory; Cancer Nanotechnology Platform Partnerships; Centers of Cancer Nanotechnology Excellence; Innovative Technologies for Molecular Analysis of Cancer; and Tumor Stem Cells in Cancer Biology, Prevention, and Therapy.

NIH provides more than $300 million per year to 65 NCI-Designated Cancer Centers (CCs) around the country. Located in almost every State, CCs provide a foundation for cancer research and offer the latest evidence-based treatment. Support is given only to institutions that have demonstrated a critical combination of exceptional scientific leadership; collaborative, multidisciplinary research; and strong institutional commitment to promoting cancer research and improving cancer care. CCs and their affiliated academic institutions are the loci for more than 50 percent of the research grants, clinical trials, training projects, and other programs that receive NCI funding. Similarly, the majority of NCI's ARRA grants go to investigators affiliated with CCs; for example, more than 60 percent of CCs participated in an ARRA-funded program to provide Summer Research Experiences for Students and Science Educators.

Given the global burden of cancer and opportunities to identify new approaches in prevention and treatment through international collaborative research, NIH is strengthening health research infrastructure and building global research capacity through the International Tobacco and Health Research and Capacity Building Program. This program promotes transdisciplinary approaches to reduce the global burden of tobacco-related illness and is designed to promote international cooperation between U.S. investigators and scientists in low- and middle-income nations where tobacco consumption is a current or anticipated public health urgency. Because the overwhelming majority of smokers begin tobacco use before they reach adulthood, the program emphasizes research on determinants of youth smoking in diverse cultural and economic settings, as well as effective ways to prevent young people from starting to smoke.

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Personalized Medicine

Although understanding of the heterogeneous nature of cancer is expanding, cancer diagnosis remains relatively nonspecific and treatment continues to be largely based on histopathology and the tissue of origin. Early successes in developing therapeutics that target specific genetic defects (e.g., Herceptin®, Gleevec®, Erbitux) have provided impetus for a more comprehensive effort to define the biological effects of the myriad genomic and other information changes that drive cancer. Advances in many critical areas of cancer research are being synthesized into a vision of a future approach to health care called "personalized medicine," which will enable clinicians to use detailed molecular and clinical information about an individual's health (including biospecimens) to guide the selection of cancer therapies or preventive measures that are most likely to be safe and effective for that person.

The NIH vision of personalized medicine spans the entire cancer continuum, from prevention through survivorship. Investments in risk assessment, treatment, and infrastructure development already have yielded progress toward realizing that vision. Potential benefits of personalized medicine include increased understanding of individual risk factors; earlier detection and more accurate diagnosis of cancer; more effective, targeted treatment; increased likelihood of survival with improved quality of life; and implementation of high-quality, patient-centered cancer care through improved communication, informatics, and surveillance.

Accelerating progress toward a new era of personalized cancer medicine will require a mix of investigator-initiated research and large-scale, high-throughput projects performed by large teams of scientists and an array of new partnerships between cancer biologists and physical scientists to move new discoveries (including advances in biospecimens, bioinformatics, proteomics, epigenomics, and emerging technologies) from the bench to the bedside.

Notable Examples of NIH Activity

Key
E = Supported through **E**xtramural research I = Supported through **I**ntramural research O = **O**ther (e.g., policy, planning, or communication) COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct IC acronyms in **bold** face indicate lead IC(s).

Initiatives and Major Programs

The Cancer Biomedical Informatics Grid® (caBIG®): The caBIG® initiative connects researchers and institutions to enable collaborative research and personalized, evidence-based care. More than 1,500 individuals representing more than 450 government, academic, advocacy, and commercial organizations have collaborated to develop a standards-based grid infrastructure (caGrid) and a diverse collection of interoperable software tools, enabling basic and clinical researchers to speed the translation of information from bench to bedside. Forty-nine of the 65 NCI-designated Cancer Centers and 8 of 10 organizations of the NCI Community Cancer Centers Program are actively deploying caBIG® tools and infrastructure in support of their research efforts. Additionally, caBIG® technology is adapted to power noncancer research initiatives such as the CardioVascular Research

Grid. Ongoing collaborations with research and bioinformation organizations in the United Kingdom, China, and India are driving international adoption of caBIG® resources. The caBIG® infrastructure also supports a new health care ecosystem, BIG Health™, in collaboration with various stakeholders in biomedicine (e.g., government, academia, industry, nonprofits, and consumers) in a novel organizational framework to demonstrate the feasibility and benefits of personalized medicine. BIG Health™ will provide the foundation for a new approach in which clinical care, clinical research, and scientific discovery are linked.

- For more information, see http://cabig.cancer.gov
- For more information, see http://bighealthconsortium.org/
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Technology Development*
- (E/I) (**NCI**)

Tobacco Control: NIH funds the Tobacco Product Assessment Consortium (TobPRAC) to develop methods and measures for product testing through a research and development contract. TobPRAC is advancing scientific knowledge about the toxic and addictive properties of tobacco products marketed by the tobacco industry with claims that imply reduced harm. In particular, this contract supports research to study the chemical and physical properties of different tobacco products, characterize the ways in which people's behavior affects their exposure to tobacco toxins, and develop methods and biomarkers to measure exposure and risk for tobacco-related diseases. The methods and findings developed under this contract will be made available to a wide range of stakeholders, including the scientific and public health communities, government, policymakers, and the general public. NIH and the American Legacy Foundation co-fund the Tobacco Research Network on Disparities (TReND). The mission of the network is to understand and address tobacco-related health disparities by advancing the science, translating that scientific knowledge into practice, and informing public policy. TReND is designed to stimulate new studies, challenge existing paradigms, and address significant gaps in research on understudied and underserved populations. It is the only national research network on tobacco and health disparities that offers a unique forum for stimulating scientific inquiry, promoting scientific collaborations, and evaluating the scientific evidence of research.

- For more information, see http://cancercontrol.cancer.gov/tcrb/tob_prod_dev.html
- For more information, see http://cancercontrol.cancer.gov/tcrb/trend/index.html
- (E) (**NCI**)

Translational Research at the Aging/Cancer Interface: The NIH Translational Research at the Aging/Cancer Interface initiative was established in 2008 to enhance research in the overlapping areas of human aging and cancer by (1) integrating knowledge of basic processes in cancer biology and aging into clinical care of older patients with cancer ("bench to bedside"), and (2) exploring clinical observations from the patient care setting at more basic and molecular levels ("bedside to bench"). Research supported by this initiative holds potential for improving prevention, diagnosis, and disease management; improving the health and well-being of older adults at risk for or diagnosed with cancer; and decreasing the functional impairment and morbidity associated with cancer in this population.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-230.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-231.html
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NIA**)

Breast Cancer and the Environment Research Centers: Researchers at the Breast Cancer and Environment Research Centers (BCERC) are investigating mammary gland development in animals, as well as in young girls, to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. These efforts hopefully will lead to strategies that better prevent breast cancer. The purpose of the centers' program is to answer questions on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Functioning as a consortium at four grantee institutions, the centers bring together basic scientists, epidemiologists, research translational units, community outreach experts, and community advocates. At one center, a sophisticated genomics and proteomics approach explores the impact of estrogenically active chemicals such as TCDD, bisphenol A, and phthalates, during early, critical periods of development. This is facilitated by advanced informatics at another major research institution. At another center, novel approaches to studying the impact of environmental exposures on interactions between epithelial cells and stromal cells are being studied. Normal and cancer-prone mice are being examined during various stages of development to determine the effects of exposure to multiple stressors as researchers are developing more sensitive screens for carcinogenicity. In concert with these studies, an epidemiological multi-ethnic study is examining and following through puberty a cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet affects adipose tissue and alters hormonal control of sexual maturation. Endocrine distruptors, irradiation, and psychosocial elements also will be studied for effects.

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- For more information, see http://www.bcerc.org/
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Epidemiological and Longitudinal Studies*, Chapter 3: *Genomics*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIEHS**, NCI) (GPRA)

The Sister Study: Environmental Risk Factors for Breast Cancer: The NIH Sister Study prospectively examines environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. The frequency of relevant genes and shared risk factors is greater among sisters, increasing the ability of the study to detect risks. Researchers will collect data on potential risk factors and current health status, and will collect and bank blood, urine, and environmental samples for future use in studies of women who develop breast cancer or other diseases compared with those who do not. Analysis of new cases will assess the separate and combined effects of environmental exposures and genetic variations that affect estrogen metabolism, DNA repair, and response to specific environmental exposures. Future analyses will focus on known and potential risk factors like smoking, occupational exposures, alcohol, diet and obesity, and include analysis of phthalates, phytoestrogens, metals, insulin, growth factors, vitamins and nutrients, and genes in blood and urine. The study also allows investigators to examine a wide range of health outcomes of relevance to women, and to create a framework from which to test new hypotheses as they emerge. In addition to its focus on genetic and environmental causes of breast cancer, the prospective Sister Study tracks changes in health status over time. Among the chronic diseases currently studied are uterine fibroids and endometriosis, rheumatoid arthritis and other autoimmune diseases, thyroid disease, asthma, and cardiovascular diseases. As the cohort ages, the Sister Study will address aging-related health outcomes including osteoporosis, Parkinson's disease, and age-related cognitive decline.

- For more information, see http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/sister/index.cfm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E/I) (**NIEHS**, NCMHD)

Surveillance, Epidemiology, and End Results (SEER): The SEER program provides essential data that support cancer research across NIH and collaborating agencies and organizations in the United States and around the world. SEER covers approximately 26 percent of the U.S. population, with information in its database on more than 5.7 million cancer cases. SEER registries routinely collect data on patient demographics, primary tumor site, morphology, extent of disease at diagnosis, and first course of treatment. All patients are followed annually for vital status and compilation of survival data. The SEER Program is the only comprehensive source of population-based data in the United States that includes stage of cancer at the time of diagnosis and survival rates by stage. It is the only population-based source of long-term incidence and survival data, having a 35-year history in most of its registries. SEER provides source data for the American Cancer Society Facts & Figures and the Annual Report to the Nation on the Status of Cancer. SEER is one of the most fundamental contributors to the cancer research infrastructure, adding more than 380,000 cases each year. The program sets national benchmarks for incidence and survival rates and is the primary source of reports on cancer death rates. The size of the database allows for analysis of rare cancers and cancer heterogeneity at both the tumor and patient level. The SEER database also includes prevalence information on the 11.4 million cancer survivors in the United States, allowing analysis by age and cancer site as well as time elapsed since

diagnosis. There are more than 2,000 agreements executed annually for the public-use data and more than 3 million hits per month on the SEER Internet homepage.

- For more information, see http://seer.cancer.gov
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E) (**NCI**)

Nanotechnology in Cancer: Nanotechnology innovation has been driven predominantly by physicists, engineers, and chemists; progress in cancer research comes primarily from discoveries of biologists and oncologists. The NIH Alliance for Nanotechnology in Cancer has set a goal of creating a community of cancer nanotechnologists who work together to develop nanotechnology approaches; apply them to the prevention, diagnosis, and treatment of cancer; and educate the medical community about opportunities enabled by cancer nanotechnology. The Alliance organized a session at 2009 American Association for Cancer Research meeting on Cancer Diagnostics Using Nanotechnology Platforms. Participants included high-profile investigators who work on the development of new nanodevices for in vitro diagnosis and in vivo imaging and clinicians who define oncology applications of those devices. Examples of this work include: PRINT, a technique allowing for controllable fabrication of nanoparticles; researching novel diagnostic techniques for proteins and DNA; developing implantable nanosensors; researching novel nanoparticle-based imaging agents and nanosensors; and developing nanotechnology-based cancer screening tools.

- For more information, see http://nano.cancer.gov/
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
- (E/I) (**NCI**)

Molecular Profiling to Tailor Cancer Treatment: Molecular profiling is a powerful tool for identifying tumor subtypes and guiding clinical decisions to optimize patient benefit. NIH programs in this area include the Strategic Partnering to Evaluate Cancer Signatures (SPECS) Program, which is evaluating the clinical utility of molecular signatures and helping translate molecular data into improved patient management, and the Lymphoma/Leukemia Molecular Profiling Project. Several studies from these and other programs demonstrate the value of tailoring cancer treatment based on molecular characteristics of the patient and tumor. Gene expression profiling revealed distinct diffuse large B-cell lymphoma (DLBCL) subtypes, one of which exhibits activation of the pro-survival NF-κB pathway. A recent study confirmed that bortezomib, a drug that indirectly prevents NF-κB activation through proteasome inhibition, selectively enhances the effects of chemotherapy in this DLBCL subtype. A recent study revealed that head and neck squamous cell carcinomas (HNSCCs) associated with human papilloma virus (HPV)-16 are more responsive to treatment than HPV-negative HNSCCs. Results from a recent clinical trial indicate that advanced colorectal cancers should be tested for mutations in the KRAS gene. Patients with tumors housing KRAS mutations are unlikely to benefit from targeted therapies that block epidermal growth factor receptor activity and should thus be spared the side effects and costs associated with these drugs. SPECS researchers recently developed an assay to classify breast cancer molecular subtypes and showed that when used in combination with clinicopathologic parameters (e.g., stage, grade), the assay improved prediction of prognosis and chemotherapy benefit.

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  Fakhry C, et al. *J Natl Cancer Institute* 2008;100(4):261-9. PMID: 18270337.
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Parker JS, et al. *J Clin Oncol* 2009;27(8):1160-7. PMID: 19204204. PMCID: PMC2667820.

- For more information, see http://www.cancerdiagnosis.nci.nih.gov/specs/index.htm
- For more information, see http://llmpp.nih.gov
- (E/I) (**NCI**)

NCI Imaging Programs: In addition to their applications in basic scientific discovery, imaging technologies contribute to cancer care through contributions to screening, diagnosis, disease staging, treatment guidance, treatment monitoring, and detection of cancer recurrence. NCI's imaging programs include the extramural Cancer Imaging Program (CIP), whose mission is to promote and support basic, translational, and clinical research in imaging sciences, and several intramural efforts within the Center for Cancer Research (CCR), such as the Molecular Imaging Program, Radiation Biology Branch, Radiation Oncology Branch, Center for Interventional Oncology, and NCI-Frederick Small Animal Imaging Program. The National Lung Screening Trial (NLST) is comparing two ways of detecting lung cancer: spiral computed tomography (CT) and standard chest X-ray. Both chest X-rays and spiral CT scans have been used to find lung cancer early. So far, neither chest X-rays nor spiral CT scans has been shown to reduce a person's chance of dying from lung cancer. This study will aim to show if either test is better at reducing deaths from this disease.

- For more information, see http://imaging.cancer.gov
- For more information, see http://home.ccr.cancer.gov/connections/features2.asp
- For more information, see http://www.cc.nih.gov/centerio/index.html
- For more information, see http://web.ncifcrf.gov/rtp/lasp/intra/saip/
- For more information, see http://www.cancer.gov/NLST
- This example also appears in Chapter 3: *Technology Development*
- (E/I) (**NCI**) (GPRA)

Experimental Therapeutics for Cancer: The NCI Experimental Therapeutics Program (NExT) is an integrated drug discovery and development effort that concentrates research into a single robust pipeline that starts with discovery of promising compounds and leads, through a series of progressive steps, to first-in-human studies. The ultimate goal is to accelerate the translation of new oncology agents to the clinic.

- For more information, see http://dctd.cancer.gov/About/major_initiatives_NExt.htm
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E/I) (**NCI**)

Education and Outreach: NCI's Office of Communications and Education (OCE) provides comprehensive cancer information to those at risk and to patients, caregivers, and health care providers. This information ranges from prevention, through treatment, to end-of-life topics. For example, clinical sites across the country extensively use NIH print- and Web-based materials to support their educational programs. OCE also provides public affairs, publications, audiovisual exhibits, and Web development support to NCI Divisions, Offices, and Centers. The Cancer Information Service (CIS) effectively communicates information through a Partnership Program to help reach those with limited access to health information; an Information Service that provides cancer information by telephone, TTY, instant messaging, and e-mail; and a Research Program that helps advance health communication practices.

- For more information, see http://www.cancer.gov/aboutnci/oce/
- For more information, see http://cis.nci.nih.gov/
- For more information, see http://cancer.gov/publications

- For more information, see http://www.cancer.gov/cancertopics
- For more information, see http://www.cancer.gov/espanol
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (E) (**NCI**)

Clinical Trials Network: NCI-supported clinical trials networks share resources and pool data to promote and support the study of new cancer treatments, methods of cancer prevention and early detection, and quality-of-life and rehabilitation issues. The 65 NCI-designated Cancer Centers serve as a major platform for these trials. NCI is restructuring the Clinical Trials Enterprise. Initiatives include: Standard Terms of Agreement for Research Trials, the Clinical Trials Reporting Program, correlative studies (e.g., biomarkers, imaging, and quality-of-life studies) embedded in clinical trials, disease-specific and patient advocate steering committees, and acceleration of translational research. The Community Clinical Oncology Program recently stopped the Selenium and Vitamin E Cancer Prevention Trial. Initial data analysis showed that selenium and vitamin E supplements, taken either alone or together for an average of 5 years, did not prevent prostate cancer. Recent findings from NCI's Cooperative Group Program include a gene abnormality that predicts childhood leukemia relapse, the role of the ch14.18 monoclonal antibody in the treatment of high-risk neuroblastoma, and the usefulness of CT colonography in detection of large adenomas and cancers. Year 2 accomplishments of the NCI Community Cancer Centers Program include increased patient and physician involvement in NCI-sponsored trials, new methods for tracking minority accrual, and improved specimen collection. The Pediatric Oncology Branch of the NCI Center for Cancer Research (CCR) is coordinating a neurofibromatosis clinical trials program to develop effective therapies for this disease. The CCR also is conducting trials for patients with androgen-independent and metastatic prostate cancer using anti-angiogenic compounds as well as novel immunotherapies and immunologic strategies.

- For more information, see http://restructuringtrials.cancer.gov/
- For more information, see http://prevention.cancer.gov/programs-resources/groups/copt/programs/about
- For more information, see http://www.cancer.gov/clinicaltrials/digestpage/SELECT/
- For more information, see http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group
- For more information, see http://target.cancer.gov/newsroom/news/01_07_09.aspx
- For more information, see http://ncccp.cancer.gov
- For more information, see http://content.nejm.org/cgi/content/full/359/12/1207
- For more information, see http://ccr.cancer.gov
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NCI**) (GPRA)

Cancer Risk Assessment, Prevention, and Early Detection: The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial is a large-scale clinical trial to determine whether certain cancer screening tests reduce deaths from prostate, lung, colorectal, and ovarian cancer. Results of a recent PLCO study revealed that men offered annual prostate specific antigen (PSA) screening were more likely to be diagnosed with prostate cancer over a 10-year period, but no more likely to die from the disease than men in a control group. These results suggest that current screening tests may result in overdiagnosis and overtreatment of prostate cancer and highlight the need for biomarkers that can more accurately identify aggressive cancers that require intervention. The PLCO Etiology and Early Marker Studies (EEMS) allow investigators to access the nearly 3 million specimens gathered through PLCO. These include biologic materials and risk factor information collected from participants prior to diagnosis of disease, which are an invaluable resource for studying the origins and modes of action of cancer and

identifying early markers of disease. The Early Detection Research Network (EDRN) is a consortium of more than 300 investigators representing divergent scientific disciplines, including genomics, informatics, and public health. EDRN was formed to facilitate the discovery, development, and validation of early detection markers and accelerate the translation of biomarker information into clinical applications. NIH also conducts a strong research program in environmental and occupation exposures to uncover elements of gene-environment interactions that can lead to increased cancer risk.

- Andriole GL, et al. *N Engl J Med* 2009;360(13):1310-9. PMID: 19297565.
- For more information, see http://www.cancer.gov/newscenter/pressreleases/PLCOProstateResults
- For more information, see http://www.parplco.org
- For more information, see http://edrn.nci.nih.gov/
- (E/I) (**NCI**)

Cancer Control P.L.A.N.E.T: The Cancer Control P.L.A.N.E.T. (Plan, Link, Act, Network with Evidence-based Tools) Web portal was launched collaboratively in 2003 by NIH, Agency for Healthcare Research and Quality, American Cancer Society, Centers for Disease Control and Prevention, Commission on Cancer, and Substance Abuse and Mental Health Services Administration. The portal now has been expanded, in collaboration with the Surveillance Action Group of the Canadian Partnership Against Cancer, to include Cancer Control P.L.A.N.E.T. Canada. The Canadian site follows the same design as the U.S. site, while engaging Canadian cancer control practitioners and researchers in usability testing to ensure that the Canadian site meets their needs. Both the Canadian and U.S. sites provide a single point of access to high-quality tools and resources from multiple national organizations that can be used to design, implement, and evaluate evidence-based cancer control plans and programs. They guide local programs to resources that help them determine cancer risk and cancer burden in their geographic areas. They also help identify potential partners and provide online resources for interpreting research findings and recommendations and accessing products and guidelines for planning and evaluation.

- For more information, see http://cancercontrolplanet.cancer.gov
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E) (**NCI**)

Brain Tumor Research: NIH funds studies aimed at understanding the development and treatment of central nervous system and peripheral nervous system tumors, including medulloblastoma, neuroblastoma, and glioblastoma, as well as research on several inherited neurological tumor syndromes, including neurofibromatosis and tuberous sclerosis complex. In the past few years NIH has released a number of funding opportunity announcements (FOAs) related to brain tumor research. A FOA on understanding and preventing brain tumor dispersal has been particularly effective in stimulating this area of research and has led to exciting advances. NIH also funds clinical studies investigating therapy delivery to the brain and evaluating the safety and tolerability of various therapies, including immunological therapies, vaccine therapy, monoclonal antibodies, and combination therapies. The Surgical and Molecular Neuro-Oncology Unit within the NIH Division of Intramural Research investigates basic mechanisms of brain tumor development and chemotherapy resistance to find new therapeutic strategies, particularly for malignant gliomas. NINDS and NCI co-lead the Trans-NIH Brain Tumor Working Group.

- For more information, see

http://www.ninds.nih.gov/find_people/groups/brain_tumor_prg/index.htm
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAS-08-048.html
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E, I) (**NINDS**, NCI)

Detection, Treatment, and Survivorship of Childhood Cancers: NIH has several ongoing programs to improve detection and treatment of childhood cancers, including the work of the NCI Pediatric Oncology Branch, the Childhood Cancer Survivors Study (CCSS), and the Pediatric Brain Tumor Consortium. Several of these programs are in collaboration with the Children's Oncology Group (COG). A recent COG study discovered that genetic alteration of the IKZF1 gene is associated with very poor outcomes in patients with B-cell progenitor acute lymphoblastic leukemia (ALL). These results should improve risk stratification for ALL patients, helping to ensure that those with high-risk disease receive treatment of appropriate intensity and sparing low-risk patients unnecessary toxic effects. The Therapeutically Applicable Research to Generate Effect Targets (TARGET) initiative is cataloguing alterations in gene expression, gene sequences, and copy number of chromosome segments in pediatric cancers to discover cancer-specific changes. TARGET data are made available to the research community through a Web portal. TARGET researchers have discovered genomic alterations in pediatric ALL that are predictive of relapse and have identified activating mutations in a tyrosine kinase gene family for which small molecule inhibitors are available. Neuroblastoma TARGET specimens were used to confirm that approximately 10 percent of high-risk neuroblastoma cases have activating mutations in another tyrosine kinase, and a pediatric Phase I trial of an inhibitor of this kinase has been developed. The success of the TARGET approach in identifying novel therapeutic targets for ALL and neuroblastoma supports extension of this approach to other childhood cancers.

- For more information, see http://www.cancer.gov/cancertopics/coping/childhood-cancer-survivor-study
- For more information, see http://www.survivorshipguidelines.org
- For more information, see http://home.ccr.cancer.gov/oncology/pediatric/
- For more information, see http://www.pbtc.org/
- For more information, see http://www.cancer.gov/NCICancerBulletin/NCI_Cancer_Bulletin_031808
- For more information, see http://target.cancer.gov
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E/I) (**NCI**) (ARRA)

Animal Models Enhance Translational Research: The Comparative Oncology Program (COP) provides an integrated mechanism by which naturally occurring cancers in pets are used to generate new information about cancer, translate biological concepts into clinical applications, and support further development of human clinical trials. The NCI Center for Applied Preclinical Research (NCI-CAPR) and the Mouse Models of Human Cancer Consortium (MMHCC) aim to accelerate the development of therapeutics and diagnostics for human diseases by providing state-of-the-art animal models genetically programmed to mimic human disease development. Researchers associated with the MMHCC recently developed genetically engineered mouse models that mimic human osteosarcoma, endometrial cancer, and melanoma. Other mouse models have been used to study the response of T cells to tumor antigens and the contributions of chronic obstructive pulmonary disease to lung cancer among smokers. MMHCC also recently launched an integrated set of bioinformatics resources in conjunction with caBIG® to support research in preclinical models. A mouse model was used to elucidate cellular responses to Myc, a protein that plays an essential role in normal cell proliferation and also has oncogenic potential. A

model of Myc-induced tumorigenesis revealed that tumor surveillance mechanisms are triggered by overexpression of the oncogene but not when the protein was deregulated without overexpression. This research provides insight into how tumor suppressor defense mechanisms can be circumvented, suggesting that keeping activated oncogenes at low levels may be important in the early stages of tumor development.

- Murphy DJ, et al. *Cancer Cell* 2008;14(6):447-57. PMID: 19061836. PMCID: PMC2723751.
- For more information, see http://ccr.nci.nih.gov/resources/cop/
- For more information, see http://emice.nci.nih.gov
- (E/I) (**NCI**)

Metabolism and Cancer: Disruptions in energy balance long have been implicated in the initiation and progression of cancer. Research on the population, organismal, cellular, and molecular levels is providing insight into the metabolic pathways that drive cancer. The Transdisciplinary Research on Energetics and Cancer (TREC) initiative supports multidisciplinary research on how obesity, poor diet, and low levels of physical activity increase cancer risk. The 96 developmental projects established to date have brought together investigators from numerous disciplines to study crosscutting problems related to energy balance and cancer. TREC's projects include molecular and animal studies of gastrointestinal, colon, and breast cancers; genetic epidemiology studies of the link between insulin resistance and colon polyps; animal and human studies of metabolic and behavioral responses to diet and exercise; and population studies to determine etiology of, or behavioral risk factors for, obesity and to assess the association of obesity, exercise, weight reduction, or diet with biomarkers. TREC is poised for expansion into other research areas, including cancer survivorship, childhood obesity, genomics, and environmental aspects of obesity. A recent study suggests that mutation of genes that code for the metabolic enzyme isocitrate dehydrogenase, which helps convert biomolecules into a form of energy usable by the cell, may be an early event in the development of some malignant gliomas. Patients with these mutations had better outcomes than those with wild type isocitrate dehydrogenase genes, suggesting that mutational analysis of these genes may be useful as a clinical diagnostic tool. Intramural research efforts are breaking ground in the field of metabolomics, the systematic identification and quantitation of all metabolites in a given organism or biological sample.

- Yan H, et al. *N Engl J Med* 2009;360(8):765-73. PMID: 19228619.
- For more information, see http://cancercontrol.cancer.gov/trec/index.html
- (E) (**NCI**)

Cancer Health Disparities Research Programs and Initiatives: NIH has expanded research on the basic biologic factors of cancer disparities to provide a foundation for minimizing risk, identifying targets, developing preventive and therapeutic interventions, and understanding how genetic susceptibility may be influenced by social, economic, race/ethnicity, and geographic factors. Thus, the research programs involve multidisciplinary teams, which contribute to understanding the etiology of cancer and build prevention and intervention evidence-based models to eliminate cancer disparities. Several programs at NIH address disparities along the cancer continuum from prevention to survival.

- The trans-disciplinary Geographic Management Program (GMaP) pilot initiative builds regional networks to support research, training, and infrastructure to develop state-of-the-art networks/centers to ensure a continuous supply of high-quality human biospecimens from multi-ethnic communities.
- The Community Networks Program engages communities experiencing cancer disparities to design,

test, and evaluate evidence-based strategies to address critical needs, such as access to screening, mentoring, and training; policy development; and community outreach and education.

- The Patient Navigation Research Program builds partnerships to ensure that racial/ethnic minorities and underserved populations with abnormal cancer screening results receive appropriate care.
- The Community Clinical Oncology Program is a network for conducting cancer prevention and treatment clinical trials by connecting academic centers with community physicians.
- The NIH Centers for Population Health and Health Disparities catalyze transdisciplinary research to improve the understanding of complex interactions of biological, social, cultural, environmental, and behavioral factors that contribute to health inequities, and to develop and implement novel intervention strategies that are multilevel and multifactorial.
- The Tobacco Research Network on Disparities' mission is to understand and address tobacco-related disparities by advancing the science, translating that scientific knowledge into practice, and informing public policy.
- The Centers of Excellence in Cancer Communication Research continue to use best practices in communication science to extend the reach of biomedical benefits equitably throughout the population.

    - For more information, see http://crchd.cancer.gov/
    - For more information, see http://crchd.cancer.gov/cnp/background.html
    - For more information, see http://crchd.cancer.gov/pnp/pnrp-index.html
    - For more information, see http://cancercontrol.cancer.gov/populationhealthcenters/cphhd/index.html
    - This example also appears in Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
    - (E) (**NCI**)

CISNET—A Resource for Comparative Effectiveness Research: The Cancer Intervention and Surveillance Modeling Network (CISNET) represents a quantum leap forward in the practice of modeling to inform clinical and policy decisions. While contemporary science has enabled the collection and analysis of health-related data from numerous sectors, enormous challenges remain to integrate various sources of information into optimal decision-making tools to inform public policy. Collaborative work on key questions promotes efficient collecting and sharing of the most important data and critical evaluation of the strengths and weaknesses of each resource. Providing results from a range of models, rather than a single estimate from one model, brings credibility to the process and reassures policymakers that the results are reproducible. CISNET is a consortium of NIH-sponsored investigators who use modeling to improve understanding of the impact of cancer control interventions (e.g., prevention, screening, and treatment) on incidence and mortality trends. The consortium's work informs clinical practice and recommended guidelines by synthesizing existing information to model gaps in available knowledge. CISNET provides a suite of models that are poised to determine the most efficient and cost-effective strategies for implementing technologies in the population. Four groups of grantees focus on breast, prostate, colorectal, and lung cancers using statistical simulation and other modeling approaches. Their models incorporate data from randomized controlled trials, meta-analyses, observational studies, epidemiological studies, national surveys, and studies of practice patterns to evaluate the past and potential future impact of these interventions.

    - For more information, see http://cisnet.cancer.gov/
    - This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
    - (E/I) (**NCI**)

Collaborations Between Minority-Serving Institutions and Cancer Centers: The Minority Institution (MI)/Cancer Center (CC) Partnership (MI/CCP) is a flagship program that has been instrumental in establishing strong collaborations between minority-serving institutions (MSIs) and CCs. MI/CCP has fostered strong cancer research partnerships throughout the United States. This program established new cancer research curricula, recruited new faculty, increased awareness about health care disparities and cultural sensitivities, and developed programs and outreach efforts in educating underserved communities. The MI/CCP has provided research education and training to individuals at all levels including postdoctoral fellows, medical students, graduate students, students at master's level, and baccalaureate and high school students. Establishing new collaborations and partnerships in communities has been a hallmark of this program, culminating in increases in numbers of awarded grant applications and numbers of manuscripts, oral presentations, and poster presentations at both regional and national levels. Many research advances are emerging from the Partnership. For example, through the Morehouse School of Medicine and University of Alabama Partnership, researchers have identified a possible genetic cause for increased risk for a more advanced form of colorectal cancer in blacks that leads to shorter survival. Understanding the relationship between molecular defects and differences in colorectal cancer incidence, aggressiveness, and clinical outcomes is important in individualizing the treatment and in eliminating racial disparities.

- For more information, see http://crchd.cancer.gov/research/miccp-overview.html
- For more information, see http://clincancerres.aacrjournals.org/cgi/content/full/15/7/2406
- This example also appears in Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (E) (**NCI**)

Training for Cancer Research: The Center for Cancer Training is preparing a workforce to advance cancer research through a scientifically integrated approach. The Center coordinates intramural and extramural research training, career development, and educational opportunities. The Interagency Oncology Task Force Joint Fellowship Program, an NIH-FDA partnership, supports development of new medical products by training scientists in research-related regulatory review. The Cancer Education and Career Development (R25T) Program supports career development for early career investigators transdisciplinary sciences, producing a generation of researchers cross-trained in disparity research areas and poised to conduct team research. The Calabresi Award in Clinical Oncology (K12) Program brings together clinicians and basic scientists to design and implement hypothesis-based therapeutic trials, promoting translation research findings from bench to beside. The Howard Temin Pathway to Independence Award in Cancer Research (K99/R00) assists early career basic scientists in transitioning from mentorship to independent research by providing funding to complete their fellowships, support their first investigator-initiated research programs, and launch their research careers. The Comparative Molecular Pathology Unit (CMPU) trains translational research investigators by incorporating interdisciplinary education in veterinary medicine with training in human biomedical research. Research Supplements to Promote Diversity in Health-Related Research create the foundation to attract and prepare qualified individuals from underrepresented and underserved populations and individuals with disabilities for careers in cancer research.

- For more information, see http://www.cancer.gov/cct
- For more information, see http://ccr.nci.nih.gov/resources/molecular_pathology/training.asp
- This example also appears in Chapter 3: *Research Training and Career Development*
- (E/I) (**NCI**)

Tumor Biology, Microenvironment, and Metastasis: The Tumor Biology and Metastasis Program supports research delineating the molecular mechanisms and signaling pathways involved in tumor progression, cell migration and invasion, angiogenesis (growth of blood vessels), lymphangiogenesis (formation of lymphatic vessels), and metastasis. Novel areas of research include the contributions of bone marrow-derived cells to tumor formation, progression, and metastasis; the role of dormant cells and their microenvironment; the role of host tissue microenvironment in organ-specific metastasis; characterization of the heterogeneity within the tumor microenvironment; and the characterization of cancer as a systemic disease. The Tumor Microenvironment Network (TMEN) investigates mechanisms of tumor-stroma interactions in human cancer. (Stroma is the connective tissue that supports or surrounds other tissues and organs.) In addition to delineating the role of host stroma in carcinogenesis, TMEN investigators are generating novel reagents that can be shared with the research community. The Cancer Immunology/Hematology Program supports research on the cellular and molecular characterization of tumor stem cells, which are minor populations of tumor cells that may be responsible for recapitulating all the cell types in a given tumor and causing metastasis due to their unique self-renewal properties. In FY 2008, NIH sponsored two RFAs on tumor stem cells aimed at enhancing synergistic research between basic scientists and translational scientists working on tumor stem cells. In addition, a program announcement for Stem Cells and Cancer was released to stimulate efforts to isolate and characterize tumor stem cells from a large spectrum of tumors to understand better the progression of malignant disease.

- For more information, see http://tmen.nci.nih.gov
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-019.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-020.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-165.html
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NCI**)

Testing for Reproductive Tumors in the National Toxicology Program's Carcinogenesis Bioassay: Perinatal Dosing: The National Toxicology Program (NTP) evaluates substances for a variety of health-related effects. Two-year studies in laboratory rodents remain the primary method by which chemicals or physical agents are identified as having the potential to be hazardous to humans. In 2006, NTP convened a workshop on Hormonally Induced Reproductive Tumors, Relevance of Rodent Bioassays to discuss the adequacy of rodent models used in the 2-year bioassay for detecting reproductive tumors. The workshop recommended that in utero and lactational exposures could be added to the chronic bioassay depending upon what is known about the mode of action. For detecting tumor types such as testicular germ cell tumors, this recommendation was especially strong. In utero and lactational exposures should be considered for mammary tumor studies if there are any developmental effects associated with a substance under study that involved endocrine tissues, steroid receptor binding, a change in mammary gland morphology, or altered timing of vaginal opening. NTP has conducted such perinatal exposures on cancer bioassays in the past, but only when there was special justification for such a design to be adopted. A new default design in which dosing will start in pregnancy and be continued throughout life or to the end of a 2-year period now has been adopted unless there is a good scientific reason not to undertake such a study. NTP has initiated studies to obtain data for constructing physiologically based pharmacokinetic (PBPK) models in rodents and nonhuman primates. It is planning studies to explore the long-term consequences of perinatal exposure to Bisphenol A to understand the potential impact to humans of the developmental changes reported in

numerous laboratory animal studies. It is hoped that the PBPK models will link information from rodent studies with primate studies, and potentially with human outcomes.

- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (O) (**NIEHS**)

Systems Biology and Systems Genetics: The Integrative Cancer Biology Program (ICBP) provides new insights into the development and progression of cancer as a complex biological system. Teams of researchers at ICBP Centers are integrating the disciplines of biology, medicine, engineering, math, and computer science (e.g., computational biology). ICBP Centers use a spectrum of innovative technologies such as genomics, proteomics, and molecular imaging to generate and validate computational and mathematical models. These in silico models describe and simulate the complex process of cancer, from the basic cellular processes through tumor growth and metastasis, and allow researchers to run "virtual" experiments, which ultimately should lead to better cancer prevention, diagnostics, and therapeutics. The centers have produced more than 35 computational models, developed a validated siRNA library of cancer genes, and created a set of nationally distributed breast cancer cell lines that reflect the heterogeneity of human breast cancer. Equally important to our understanding of cancer is systems genetic research (systems biology + genetics). Networks of genes can be found and their associations tested and quantified with parallel association studies on relevant human populations.

- For more information, see http://icbp.nci.nih.gov/
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NCI**)

Health Care Delivery Consortia to Facilitate Discovery and Improve Quality of Cancer Care: The purpose of the Cancer Research Network (CRN) is to enhance research on cancer epidemiology, prevention, early detection, and control in the context of health care delivery systems. CRN combines established research groups affiliated with 14 health care delivery organizations that provide comprehensive care to a racially and ethnically diverse population of nearly 11 million individuals. CRN has developed strong research capabilities in several areas: developing and applying innovative methods to collect and interpret data from both conventional and electronic medical records systems; assembling large samples of patients with documentation of patient characteristics and longitudinal data on receipt of health services and clinical and quality-of-life outcomes; collecting and integrating complex data from patients, providers, and organizations to examine issues in health care delivery from multiple perspectives; quantifying the effect of key factors in the delivery process that may determine quality and outcomes of care; and conducting studies on behavioral and systems-based interventions to improve the delivery of care in community-based health care delivery systems. The Breast Cancer Surveillance Consortium (BCSC) is a research resource for studies designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. The BCSC is a collaborative network of seven mammography registries with linkages to tumor and/or pathology registries. The Consortium's database contains information on 7,521,000 mammographic examinations, 2,017,869 women, and 86,700 cancer cases.

- For more information, see http://crn.cancer.gov
- For more information, see http://breastscreening.cancer.gov/

- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*, Chapter 3: *Clinical and Translational Research* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (I) (**NCI**)

HIV/AIDS-Related Malignancies: The Activities to Promote Research Collaborations in AIDS-Associated Malignancies initiative provides administrative supplements for multidisciplinary collaborations among NCI grantees and AIDS investigators. Recently issued program announcements solicit applications to advance understanding of the risks, development, progression, diagnosis, and treatment of malignancies observed in individuals with underlying HIV infection or AIDS. One of these focuses on the role of HIV/AIDS in the etiology, prevention, and treatment of hepatocellular carcinoma. The Fogarty International Clinical Research Scholars Program pairs U.S. students with students from low- and middle-income countries (LMICs) to conduct research on AIDS-related malignancies in LMICs. The goal is to build research capacity in both countries and build intellectual bridges between the United States and LMICs. HIV/AIDS and cancer registries in three states were linked to study cancer risk among HIV-infected persons (initially AIDS-free) over time. Kaposi sarcoma and non-Hodgkin lymphoma incidence have declined markedly in recent years, likely reflecting treatment-related improvements in immunity, while incidence of some non-AIDS-defining cancers have increased. A study of nearly 500,000 individuals diagnosed with AIDS revealed that the risk of human papillomavirus (HPV)-associated cancers is increased among persons with AIDS and that this risk rises with increasing immunosuppression. Persons with AIDS also were found to be at increased risk for melanoma, Merkel cell carcinoma, and sebaceous carcinoma. The U.S. HIV/AIDS Cancer Match Study found that risk of sqamous cell carcinoma of conjunctiva and other eye cancers is increased among adults with AIDS.

- Engels EA, et al. *Int J Cancer* 2008;123(1):187-94. PMID: 18435450.
  Guech-Ongey M, et al. *Int J Cancer* 2008;122(11):2590-3. PMID: 18224690.
  Lanoy E, et al. *AIDS* 2009;23(3):385-93. PMID: 19114864. PMCID: PMC2728602.
  Chaturvedi AK, et al. *J Natl Cancer Inst* 2009;101(16):1120-30. PMID: 19648510. PMCID: PMC2728745.
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-454.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-243.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-244.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-245.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-455.html
- For more information, see http://www.cancer.gov/cancertopics/types/AIDS
- For more information, see http://oham.cancer.gov
- (E) (**NCI**, FIC)

Genome-Wide Association Studies: With unprecedented speed, researchers have used an approach called genome-wide association studies (GWAS) to explore genetic variants and their complex relationships to human health and disease. GWAS research has linked a stunning number of genetic variants to common conditions—more than 130 in 2008 alone. For example, the obesity epidemic and its related health conditions pose a great challenge for the Nation. In 2008, the Genetic Investigation of Anthropometric Traits consortium identified six genes associated with body mass index, a key indicator for obesity. Also in 2008, three GWAS of lung cancer implicated several genes already known to be linked to nicotine addiction. In a feat that would not have been possible without the power of whole genome analysis, the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium in 2009 gathered data from participants in long-running studies to reveal genetic variants associated with an increased risk of stroke. Identification of genetic variants associated with common diseases opens

new windows into the biology of health and disease. This work also raises the possibility of someday using genetic testing, in combination with family history, to identify at-risk, pre-symptomatic individuals who might benefit from personalized screening and preventive therapies.

- For more information, see http://www.genome.gov/27528559
- For more information, see http://www.genome.gov/27529231
- For more information, see http://www.genome.gov/27531390
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Genomics* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E, I) (**NHGRI, NIDDK, NCI, NIA, NHLBI, NIMH**, NINDS)

Exemplary Current Studies and Projects

Genome-Wide Association Studies of Cancer Risk: The Cancer Genetic Markers of Susceptibility (CGEMS) project is a signature initiative that uses genome-wide association studies (GWAS) to identify genetic variants and mechanisms associated with cancer risk. Understanding these variants and mechanisms may lead to new preventive, diagnostic, and therapeutic interventions. CGEMS investigators have pinpointed genetic variants associated with elevated prostate cancer risk as well as variants associated with increased breast cancer risk. The same genetic variant was shown to be involved in increased prostate, colon, and other cancers, suggesting a common mechanistic pathway for susceptibility to a variety of cancers. Another GWAS project, the Cohort Consortium, is a unique extramural/intramural collaboration that allows Consortium partners to share access to data on 37 cohorts comprised of 4 million people from diverse populations. Each cohort contains extensive information on known or suspected risk factors and biospecimens collected pre- and post-diagnosis. The large number of study subjects permits the detection of modest genetic effects, as well as studies of variants involved in less common cancers. One cohort within the Consortium, the Prostate, Lung, Colorectal, and Ovarian (PLCO) cohort, includes about 2.9 million specimens. These pre-diagnostic specimens provide a valuable resource for studies of cancer etiology and early detection. Researchers can correlate changes in molecular profiles associated with the onset of different types of disease, thereby providing valuable insights into the actual mechanisms of human carcinogenesis.

- For more information, see http://cgems.cancer.gov
- For more information, see http://epi.grants.cancer.gov/Consortia/cohort.html
- For more information, see http://www.parplco.org
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*
- (E/I) (**NCI**)

Development of Image-Guided Interventions: Image-guided interventions (IGI) provide therapy that can minimize trauma and improve patient outcomes. They are applicable in procedures such as biopsy, surgery, radiation treatment, vascular interventions, and guidance during delivery of devices, drugs, cells, or genes. These improved capabilities particularly are important in light of the shifting trend in medicine toward a model of early, presymptomatic detection of disease. Representative of ongoing research is an effort to improve image-guided surgical removal of tissue using optical coherence tomography (OCT). Recent studies suggest that OCT optical imaging techniques may have a significant impact on breast cancer biopsy and treatment. High-resolution OCT image guidance could help ensure complete surgical removal of tumors and adequate diagnostic biopsy sampling. As other biomedical

imaging modalities, such as MRI, improve the ability to detect small suspicious lesions, OCT can be used to guide a biopsy needle precisely to tumor tissue and cells and enable sampling of these smaller nonpalpable lesions. In preliminary studies, surgically removed lumpectomy specimens from more than 65 patients have been imaged with OCT in the operating room. When compared to post-operative histopathology, OCT yielded a sensitivity of 100 percent and a specificity of 82 percent and demonstrates the potential of OCT as a real-time method for the intraoperative margin assessment in breast-conserving surgeries.

- Nguyen FT, et al. Meeting Abstract: Optical coherence tomography (OCT) as a diagnostic tool for the real-time intraoperative assessment of breast cancer surgical margins. *Cancer Res* 2009;69: 802.
- This example also appears in Chapter 3: *Technology Development*
- (E) (**NIBIB**) (GPRA)

Cancer Epidemiology Biomarkers and Prevention: The long-term Sister Study looks at the environmental and genetic characteristics of women whose sisters have had breast cancer to identify factors associated with developing breast cancer. A pilot study that was part of the Sister Study shows that women who maintain a healthy weight and who have lower perceived stress may be less likely to have chromosome changes associated with aging than obese and stressed women.
Recently, NIH funded a study looking at 94 women whose breast cancer had spread or returned. Researchers asked the women whether they had ever experienced stressful or traumatic life events. The categories ranged from traumatic stress to some stress to no significant stress. The comparison revealed a significantly longer disease-free interval among women reporting no traumatic or stressful life events.

- For more information, see http://www.niehs.nih.gov/news/releases/2009/sister-study.cfm
- For more information, see http://www.nlm.nih.gov/medlineplus/magazine/issues/winter08/articles/winter08pg6b.html
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
- (E/I) (**NCI**, NIA)

Microchip Captures Early Circulating Cancer Cells: Malignant cancers shed cells that enter the circulation, travel to other areas of the body, and often grow into secondary tumors, or metastases. Indeed, metastases are responsible for the great majority of cancer deaths. It is estimated that 70,000 men per year are diagnosed with recurrent prostate cancer after prostatectomy, as shown by rising prostate surface antigens. For these men, the ability to detect and characterize the malignant cells in the blood may enable personalized therapy. Researchers are developing a technology to facilitate quantitative detection of circulating tumor cells (CTCs). They have engineered a microchip with a large surface area of an adhesion molecule that binds CTCs from whole blood, making detection of CTCs more reliable than previous approaches. They are analyzing molecular and genomic information in the CTCs to identify new biomarkers to customize treatments that are personalized for the patients and to predict treatment outcomes. The NIH-supported research has the potential to eliminate or greatly reduce cancer deaths due to metastases.

- Nagrath S, et al. *Nature* 2007;450(7173):1235-9. PMID: 18097410.
- For more information, see http://www.nibib.nih.gov/HealthEdu/eAdvances/31July08
- This example also appears in Chapter 3: *Technology Development*

- (E) (**NIBIB**)

Molecular Theranostics: New Technologies for the Diagnosis and Treatment of Diseases: The concept of combining a therapeutic with a diagnostic agent rapidly is evolving and goes beyond traditional diagnostic tests that screen or confirm the presence of a disease. With specialized molecular imaging techniques and biomarkers, theranostics might predict risks of disease, diagnose disease, and monitor therapeutic response leading to real-time, cost-effective treatment. NIH supports a number of teams that are developing novel theranostics and approaches that can be applied in clinical studies of human patients. A team of chemists and neurosurgeons at the University of Michigan is developing highly specific, dye-loaded nanoparticles capable of delivering targeted photosensitizers to improve the survival of brain tumor patients. This technique will allow neurosurgeons to visualize the brain tumors for surgical resection of the main tumor mass while eradicating remaining tumor cells through a process known as photodynamic therapy. These particles also contain imaging contrasting agents to visualize response to therapy.

- This example also appears in Chapter 3: *Technology Development*
- (E) (**NIBIB**)

Cell Senescence and Aging: Cell senescence is a mechanism prominent in aging processes and widely considered as an anti-cancer preventive or treatment therapy. Studies focus on such topics as senescence induced by the Ras gene and its potential to halt or slow tumor progression, the role of the retinoblastoma protein pRb in cellular senescence and the development of a wide range of cell types and associated tumors, telomere attrition, the role of oxidative stress, epigenetic regulation, and DNA damage and repair. NIA-supported studies on Werner syndrome (a condition characterized by accelerated aging in children) and the role of the WRN protein in telomere metabolism are improving our understanding of basic cellular mechanisms that act to suppress development of specific aging characteristics and cancer.

- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
- (E/I) (**NIA**)

New Biomaterials System Programs Cells in situ to Fight Cancer: In the body's immune response to foreign invaders, dendritic cells signal and activate other cells to initiate a generalized inflammatory response. Cell-based cancer vaccinations build on this natural tendency by isolating and activating a patient's dendritic cells using tumor antigens, and then injecting the reprogrammed cells back into the patient. The activated dendritic cells travel home to the lymph nodes and promote an antitumor response. Unfortunately, most transplanted dendritic cells die. Additionally, reprogrammed cells partially lose their effectiveness after injection back into the body. Thus, multiple rounds of injections are required to achieve significant effect. To address these limitations, investigators developed a multifunctional in situ dendritic cell reprogramming system composed of polymeric biomaterials that release cytokines to attract dendritic cells already within the lymph nodes into the biomaterials. The dendritic cells are then activated by the biomaterials. The biomaterials reduce their cytokine release at a controlled rate so that after activation, the dendritic cells will migrate away from the biomaterials back home to the lymph nodes and present tumor antigens to T cells found there. In a mouse model this sophisticated system provided protection from tumor development equal or superior to that provided by traditional cancer vaccines without the complications and costs of ex vivo cell manipulation and

transplantation. The new system also provided much better control over the number of dendritic cells than traditionally generated cancer vaccines. This study demonstrates a powerful new application for polymeric biomaterials that could be used in the future against cancers and other diseases.

- Ali OA, et al. *Nature Materials* 2009;8(2):151-8. PMID: 19136947. PMCID: PMC2684978.
- This example also appears in Chapter 3: *Technology Development*
- (E) (**NIDCR**)

New Model Reveals Novel Molecular Strategies in the Fight to Overcome Oral Cancer: Oral and pharyngeal carcinomas are the ninth most common cancer worldwide, with more than 35,000 new patients and more than 7,500 deaths each year in the United States alone. The 5-year survival rate has improved only marginally over the past 40 years. There is an urgent need for new options for these patients. Emerging information on the deregulation of normal molecular mechanisms that result in the cancer's progression provides the possibility of new mechanisms-based therapeutic approaches for these aggressive oral malignancies. NIH scientists recently used a two-step chemical carcinogenesis model and found that the drug rapamycin exerted a remarkable anticancer activity. It decreased the tumor burden of mice having early and advanced tumors, and even brought about the regression of recurrent squamous cell skin cancers. The scientists reported that the persistent activation of mTOR, the mammalian Target of Rapamycin, occurs frequently in head and neck cancer patients and that its inhibition by rapamycin causes regression of human oral cancer tumors implanted in mice. Because chemically induced animal cancer models often better reflect the complexity of the clinical setting, the scientists developed an oral-specific chemical carcinogenesis mouse model. In this model, activation of mTOR is an early event in precancerous lesions; rapamycin treatment can halt the malignant conversion of precancerous lesions and promote the regression of advanced carcinogen-induced oral squamous cell carcinomas (SSCs). Significance: The development of this SCC carcinogenesis model demonstrates that the use of mTOR inhibitors may provide a novel molecular-targeted strategy for chemoprevention and treatment of oral squamous cell cancer.

- Amornphimoltham A, et al. *Clin Cancer Res* 2008;14(24):8094-101. PMID: 19073969. Czerninski R, et al. *Cancer Prevention Res* 2009;2(1):27-36. PMID: 19139015.
- For more information, see http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/OralCancer/
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (I) (**NIDCR**)

New Targets Identified for Intervention in the Development of Head and Neck Cancers: Over the last decade, cancer researchers have made significant progress in defining the molecular pathways involved in the development of head and neck squamous cell cancer. Studies that identify and characterize "key players" hold tremendous promise for the future treatment of these devastating cancers and ultimately improve the overall survival and quality-of-life for afflicted patients. One such key player is a family of proteins known as Wnt. Aberrant activation of the Wnt pathway has been found to be associated with cancer development and progression. Wnt promotes initiation of cancer by increasing the nuclear accumulation of ß-catenin, an integral component of Wnt signaling, to activate target genes downstream. However, the mechanism of ß-catenin recruitment to the Wnt target gene promoter largely is unknown. In an elegant study, the researchers discovered that ß-catenin interacted with two other molecules (commonly called TBL1 and TBLR1), leading to the recruitment of ß-

catenin to the promoter of Wnt target genes. Decreasing TBL1 or TBLR1 via genetic knock-down did not affect the nuclear accumulation of ß-catenin, but it did inhibit ß-catenin significantly from binding to Wnt target gene promoter and the expression of Wnt target genes associated with tumor development. Moreover, depletion of TBL1 or TBLR1 inhibited invasive growth of tumor cells. These results provide fundamental knowledge about tumor genesis by revealing two new components required for nuclear ß -catenin function. Targeting these molecules can have important therapeutic implications for head and neck cancer.

- Li J, Wang C-Y. *Nat Cell Biol* 2008;10(2):160-9. PMID: 18193033.
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (E) (**NIDCR**)

Inflammation, Immunology, and Cancer Virology: Several NIH programs are working to facilitate and rapidly translate advances in the discovery, development, and delivery of immunologic and antiviral approaches to improve the prevention and treatment of cancer, cancer-related viral diseases, and AIDS-associated malignancies. One notable example with implications for therapeutic cancer vaccine development is the discovery that co-delivery of Interleukin (IL)-15 with vaccines results in a more robust immune response both at the time of vaccine administration and in the event that the target antigen is encountered a second time. (IL-15 is a protein that regulates activation and proliferationn of some cells in the immune system.) IL-15 currently is in production for large-scale clinical trials. The human papillomavirus (HPV) Vaccine Trial in Costa Rica is a multiyear effort designed to test the ability of virus-like particle vaccines, originally developed at NIH, to protect against HPV16/18 infection. In addition to evaluating vaccine efficacy, the trial is examining broader measures of vaccine impact as well as immunity, natural history of HPV, and cervical neoplasia.

- Oh S, et al. *Proc Natl Acad Sci U S A* 2008;105(13):5201-6. PMID: 18362335. PMCID: PMC2278231.
- For more information, see http://ccr.nci.nih.gov
- For more information, see http://home.ccr.cacner.gov/coe/immunology/
- For more information, see https://ccrod.cancer.gov/confluence/display/CEHCV/Home
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E/I) (**NCI**, NIAID, OAR, ORWH)

Massage Therapy May Ease Pain and Improve Mood in Advanced Cancer Patients: People with advanced cancer often experience pain that causes physical and emotional distress, which leads to a decrease in functional ability and quality of life. Symptom relief is an important part of end-of-life care, and small studies have suggested that massage therapy may benefit people with advanced cancer. In a study funded in part by NIH, researchers investigated the benefits of massage vs. simple touch therapy (placing both hands on specific body sites) in patients with advanced cancer. This multisite study—conducted at 15 U.S. hospices in the Population-Based Palliative Care Research Network—included 380 participants with advanced cancer who were experiencing moderate to severe pain. Participants were randomly assigned to receive 6 30-minute treatment sessions of either massage or simple touch therapy over a 2-week period. The study found that both the massage and simple touch groups experienced statistically significant improvements in pain relief, physical and emotional distress, and quality of life. Immediate improvement in pain and mood was greater with massage than with simple touch; however, sustained effects of these therapies were not observed. The study's findings indicate that massage therapy may provide some immediate relief for patients with advanced cancer. The

findings also suggest that simple touch, which can be provided by family members and volunteers, may benefit these patients.

- Kutner JS, et al. *Ann Intern Med* 2008;149(6):369-79. PMID: 18794556. PMCID: PMC2631433.
- For more information, see http://nccam.nih.gov/research/results/spotlight/110608.htm
- (E) (**NCCAM**)

Other Notable Examples

2009 Institute of Medicine Report, The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors: The recently released IOM report, *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors,* reviews U.S. interest and investment in global health. This report is particularly timely and useful given the major changes in global health that have occurred since the last IOM report, *America's Vital Interest in Global Health: Protecting Our People, Enhancing Our Economy, and Advancing Our International Interests*, was released in 1997. These changes include unprecedented interest and large fiscal commitments to global health by the U.S. government and nongovernmental sectors. The IOM leveraged the contributions of 18 NIH ICs to undertake this update with additional financial support from several key private and public entities. The study makes the case for why U.S. agencies and private sector entities should invest more heavily in global health. The report has five key recommendations that can inform NIH investments in global health in the coming years:

- Scale up existing interventions to achieve significant health gains
- Generate and share knowledge to address health problems endemic to the global poor
- Invest in people, institutions, and capacity-building with global partners
- Increase U.S. financial commitments to global health
- Set the example of engaging in respectful partnerships

The IOM panel was chaired by Dr. Harold Varmus and Ambassador Thomas Pickering. A preliminary report, titled *The U.S. Commitment to Global Health: Recommendations for the New Administration*, was released in December 2008. In May 2009, the final report, titled *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors*, was released.

- For more information, see http://www.iom.edu/Reports/2009/The-US-Commitment-to-Global-Health-Recommendations-for-the-Public-and-Private-Sectors.aspx
- For more information, see http://www.iom.edu/Reports/2008/The-US-Commitment-to-Global-Health-Recommendations-for-the-New-Administration.aspx
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (O) (**FIC**, NCCAM, NCI, NCRR, NEI, NHGRI, NHLBI, NIAAA, NIAID, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINDS)

Research Tools for Genomic Studies of Cancer: The Cancer Genome Atlas (TCGA) is developing a publicly accessible, comprehensive catalog of the many genetic changes that occur in cancers. Tumor and matched normal samples are analyzed for genetic changes such as chromosome rearrangements and gene mutations; gene expression changes, including changes in expression patterns of microRNAs, as well as epigentic modifications (differences in the chemical modifications of

DNA that influence gene expression). All data, including pre-publication data, are freely available through the TCGA website and are compatible with the cancer Bioinformatics Grid (caBIG®). The first TCGA project, which focused on brain cancer (glioblastoma multiforme), demonstrated the feasibility and impact of large-scale NIH-coordinated cancer genome analysis. Comprehensive characterization of ovarian cancer with other tumor types will follow. The goal of the Cancer Genome Anatomy Project (CGAP) is to provide cancer researchers with tools, resources, and information derived from studies that are characterizing differences between cancer and normal cells. The CGAP website provides access to data, bioinformatic tools, and information about available full-length cDNAs and short hairpin RNA clones. These resources are helping scientists conduct the research necessary to improve detection, diagnosis, and treatment of cancer. In the past year, new projects that explore molecular characterization through novel technologies were added as part of the Cancer Genomic Technology Initiative (CGTI). REMBRANDT is the national portal for molecular, genetic, and clinical data associated with several thousand primary brain tumors. This framework provides researchers the ability to answer basic questions related to a patient or patient populations and view integrated datasets in a variety of contexts.

- For more information, see http://cancergenome.nih.gov/index.asp
- For more information, see http://cgap.nci.nih.gov/
- For more information, see https://caintegrator.nci.nih.gov/rembrandt/
- For more information, see http://www.ninds.nih.gov/find_people/groups/brain_tumor_prg/index.htm
- This example also appears in Chapter 3: *Genomics*
- (E/I) (**NCI, NHGRI**, NINDS) (ARRA)

NIH Strategic Plans Pertaining to Cancer

National Cancer Institute (NCI)

- *NCI Strategic Plan for Leading the Nation*
- *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2008*
- *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2009*
- *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2010*
- *Advancing Basic, Translational and Clinical Research: A Strategic Plan for the Center for Cancer Research*

National Institute of Dental and Craniofacial Research (NIDCR)

- *NIDCR Strategic Plan*
- *NIDCR Implementation Plan*

National Center for Complementary and Alternative Medicine (NCCAM)

- *Expanding Horizons of Health Care: Strategic Plan 2005-2009*

John E. Fogarty International Center (FIC)

- *Pathways to Global Health Research: Strategic Plan 2008-2012*

Office of AIDS Research (OAR)

- *FY 2008 Trans-NIH Plan for HIV-Related Research*
- *FY 2009 Trans-NIH Plan for HIV-Related Research*
- *FY 2010 Trans-NIH Plan for HIV-Related Research*

Other Trans-NIH Plans

- *Report of the Brain Tumor Progress Review Group*
  (NCI, NINDS)